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# Variable Response to a Long-Acting Agonist of Luteinizing Hormone-Releasing Hormone in Girls with McCune-Albright Syndrome

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**ABSTRACT.** Six girls with McCune-Albright syndrome were treated for at least 2 months with the long-acting LHRH agonist D-Trp$^6$-Pro$^9$-NEt-LHRH, which previously was found to be an effective treatment for true precocious puberty. Nocturnal and LHRH-stimulated serum gonadotropin levels and plasma estradiol levels were measured before treatment and after 2–3 months of treatment. Five of the six girls had no decrease in serum gonadotropin or plasma estradiol levels during therapy, and their pubertal signs were unaffected by treatment. All five of these girls had serum gonadotropin levels that were within or below the normal prepubertal range. The sixth girl, who had gonadotropin levels in the normal pubertal range before treatment, had decreased serum gonadotropin and plasma estradiol levels during 1 yr of LHRH analog therapy. This was associated with cessation of menses and regression of secondary sexual changes. The failure of LHRH analog to modify the course of precocious puberty in the five patients with prepubertal serum gonadotropin concentrations is further evidence that the mechanism of precocious puberty in most girls with McCune-Albright syndrome differs from that in patients with true precocious puberty. (*J Clin Endocrinol Metab* **59:** 801, 1984)

PATIENTS with McCune-Albright syndrome have precocious puberty, fibrous dysplasia of bone, and café-au-lait skin pigmentation (1). Variant forms of McCune-Albright syndrome, where only two of the three above findings are present, also have been recognized (2). The underlying mechanism of precocious puberty in girls with McCune-Albright syndrome has been attributed to apparent autonomous ovarian function (precocious pseudopuberty) with low serum gonadotropin levels (2–8) or to premature activation of the hypothalamic-pituitary-ovarian axis (true precocious puberty) (2, 9–11).

We previously reported the clinical and hormonal findings in six girls with McCune-Albright syndrome (12). In the current study, we attempted to treat the sexual precocity in these children with a long-acting LHRH agonist, D-Trp$^6$-Pro$^9$-NEt-LHRH (LHRH$_a$), which has been successfully used to suppress the elevated gonadotropin and sex steroid concentrations and to correct the rapid growth and bone age advancement in girls with idiopathic true precocious puberty (13–15). The girls with McCune-Albright syndrome had variable responses of serum gonadotropin and estradiol concentrations to treatment with LHRH$_a$.

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## Materials and Methods

### *LHRH analog*

LHRH$_a$, provided by Drs. Wylie Vale and Jean Rivier of the Salk Institute (La Jolla, CA) was dissolved in normal saline and 10% mannitol (14). The stability of the compound at −20 C, during refrigeration, and during mild heating was previously demonstrated (16).

### *Subjects*

The clinical and radiographic data that supported the diagnosis of McCune-Albright syndrome are summarized in Table 1. Patients 1 and 3 had extensive lower limb bone deformities, with subsequent height loss due to fibrous dysplasia of bone. Patients were included in the study only after exclusion of brain, adrenal, or ovarian neoplasms by computed tomography of the head and ultrasonography of pelvic and adrenal regions. The ovaries of all six patients were enlarged compared to those of prepubertal girls, and the left ovary of patients 2 and 4 contained large cysts measuring 1–3 cm in diameter (12). Plasma 17-hydroxyprogesterone and 11-deoxycortisol, measured to exclude congenital adrenal hyperplasia, were normal.

TABLE 1. Clinical and radiographic data

| Patient no. | Age (yr) | Bone age (yr) | Ht | | Stages of puberty[a] | | Menses[b] | Café-au-lait pigmentation[b] | Bone lesions[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | | cm | % | Breast | Pubic hair | | | |
| 1 | 4.5 | 7.8 | 107 | 60 | III | IV | + | + | + |
| 2 | 5.1 | 8.8 | 128 | >97 | IV | III | + | + | + |
| 3 | 5.2 | 6 | 102 | 25 | II | II | + | + | + |
| 4 | 1.2 | 2 | 82 | 95 | III | I | + | — | + |
| 5 | 4.5 | 6.8 | 117 | >97 | IV | II | + | — | + |
| 6 | 8.9 | 13.5 | 152 | >97 | IV | III | + | — | + |

[a] Stages of puberty according to Tanner (24).
[b] +, Present; —, absent.

Serum $T_4$, free $T_4$, and TSH levels were normal.

Six normal 2- to 10-yr-old girls (mean age, 6.4 yr) with Tanner stage I breast and pubic hair development were studied to obtain normal prepubertal values for nocturnal gonadotropin concentrations. LHRH-stimulated gonadotropin concentrations were determined in four of the normal girls. Eight normal 12- to 15-yr-old girls with Tanner stage III–IV pubic hair and breast development were studied to obtain normal pubertal nocturnal and LHRH-stimulated gonadotropin concentrations.

*Protocol*

Patients were admitted to the Clinical Center of the NIH. The protocol was approved by the Clinical Research Committee of the NICHHD. Informed consent was obtained from a parent, and assent was obtained from children above age 7 yr. Serum gonadotropin concentrations were measured every 20 min from 1000–1400 h (daytime levels) and 2200–0200 h (nocturnal levels). Plasma estradiol concentrations were measured at the beginning and end of each period of gonadotropin sampling. On day 2, a LHRH stimulation test was performed. LHRH (100 $\mu$g) was injected iv at time zero, and serum gonadotropin levels were measured at −30, −15, 0, 15, 30, 45, 60, 90, 120, and 180 min. After the initial studies, children were given daily sc injections of $LHRH_a$ at a dose of 4 $\mu$g/kg·day for 8–12 weeks. Eight weeks of $LHRH_a$ therapy was previously shown to suppress serum gonadotropin levels in girls with idiopathic precocious puberty (13–15). After 8–12 weeks, the children were readmitted to the Clinical Center, and the hormone measurements described above were repeated.

*Hormone assays*

Serum LH, FSH, and estradiol were measured by modifications of previously described methods (16–19). The sensitivity limits for these assays were 0.3 mIU/ml (Second International Reference Preparation of human menopausal gonadotropin), 0.2 mIU/ml, and 20 pg/ml, respectively. Intraassay and interassay coefficients of variation were 7% and 12% for LH, 5% and 14% for FSH, and 8% and 16% for estradiol. Hormonal measurements before and during treatment were performed in separate assays for each patient.

*Statistical analysis*

All data are represented as the mean ± SEM. Statistical comparisons were made by Student's $t$ test.

## Results

*Effect of $LHRH_a$ on serum gonadotropin levels*

The nocturnal serum gonadotropin levels before treatment for patients 1–5 were significantly below the levels in the normal prepubertal girls ($P < 0.05$ for LH; $P < 0.01$ for FSH; Fig. 1A). These levels did not decrease during treatment with $LHRH_a$. The peak serum gonadotropin response to LHRH treatment in patients 1–5 was within the normal prepubertal range for LH (Fig. 2A), but was significantly below normal for FSH ($P < 0.01$; Fig. 2C). The peak gonadotropin levels after LHRH were not significantly suppressed during $LHRH_a$ ther-

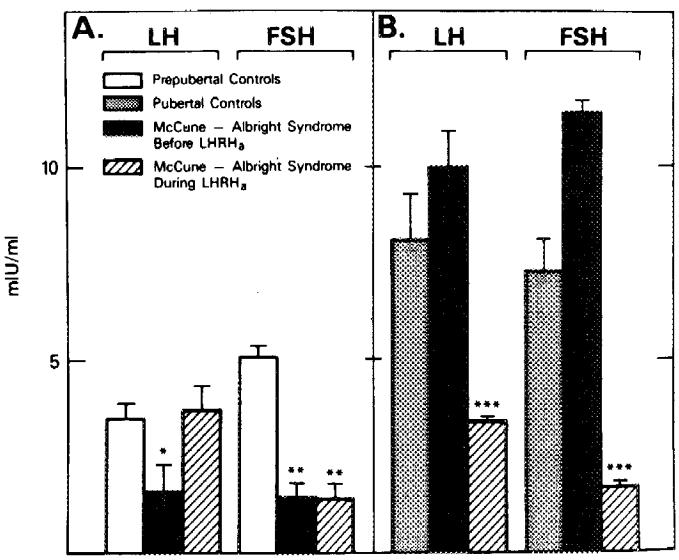


FIG. 1. Nocturnal serum LH and FSH levels in normal girls and in girls with McCune-Albright syndrome. A, Patients 1–5, before and during $LHRA_a$ administration (2–3 months of treatment), and prepubertal controls. The nocturnal LH and FSH levels in each subject were the means of 13 measurements obtained every 20 min from 2200–0200 h. The *bars* show the mean ± SEM of the nocturnal LH and FSH levels for the five patients and controls. B, Patient 6 and normal pubertal controls. The *error bars* for patient 6 are the SEM for the 13 LH and FSH levels from 2200–0200 h. *, $P < 0.05$; **, $P < 0.001$ (compared to prepubertal controls). ***, $P < 0.001$ (compared to the pretreatment level in patient 6).

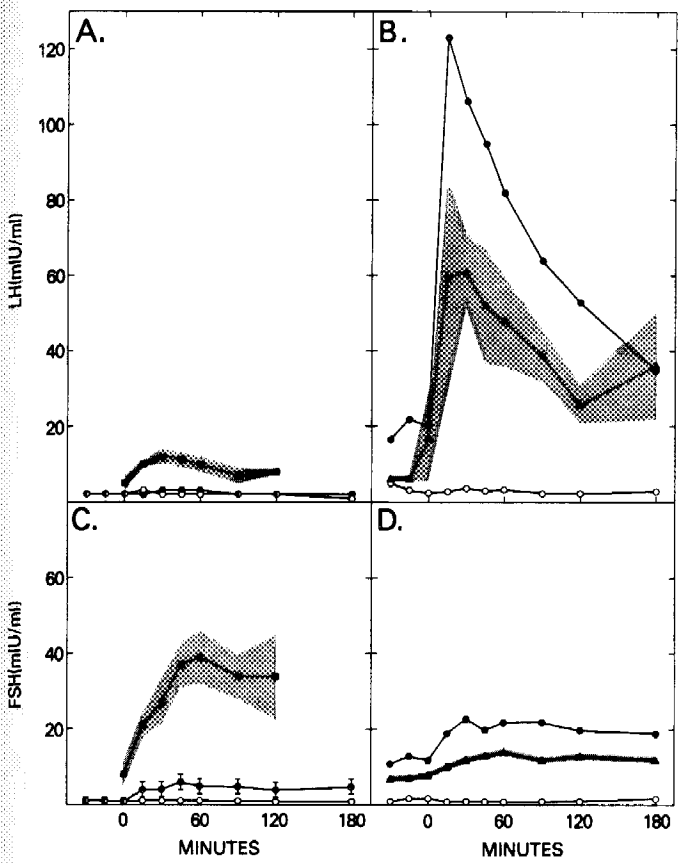


FIG. 2. Gonadotropin concentrations in response to 100 μg LHRH given iv at time zero. ●—●, Before therapy; ○—○, during therapy for 8–12 weeks. ■– –■, mean of values from four normal prepubertal girls; ▲– –▲, mean of values from seven pubertal girls. *Shaded areas* represent the mean ± SEM. A, Response of LH in patients 1–5. B, Response of LH in patient 6. C, Response of FSH in patients 1–5. D, Response of FSH in patient 6.

apy. $LHRH_a$ therapy in patient 6, however, who had normal pubertal nocturnal gonadotropin levels and a pubertal response to LHRH before treatment, suppressed both nocturnal gonadotropins ($P < 0.001$ for LH and FSH; Fig. 1B) and the peak gonadotropin response to LHRH (Fig. 2, B and D).

### *Effect of $LHRH_a$ on plasma estradiol levels*

Estradiol levels in patients 1–5 either remained unchanged or rose during $LHRH_a$ therapy (Fig. 3). Despite low gonadotropin levels during $LHRH_a$ treatment, cyclic variation in plasma estradiol occurred in patient 4 (Table 2) and was described previously in patient 2 (20). Only patient 6, who had basal and LHRH-stimulated gonadotropin levels within the normal pubertal range, had a fall in plasma estradiol concentrations during treatment with $LHRH_a$ (Fig. 3).

### *Effects of $LHRH_a$ on secondary sexual characteristics*

Patients 2, 3, 4, and 6 were treated with $LHRH_a$ for 1 yr. Secondary sexual characteristics failed to regress, and

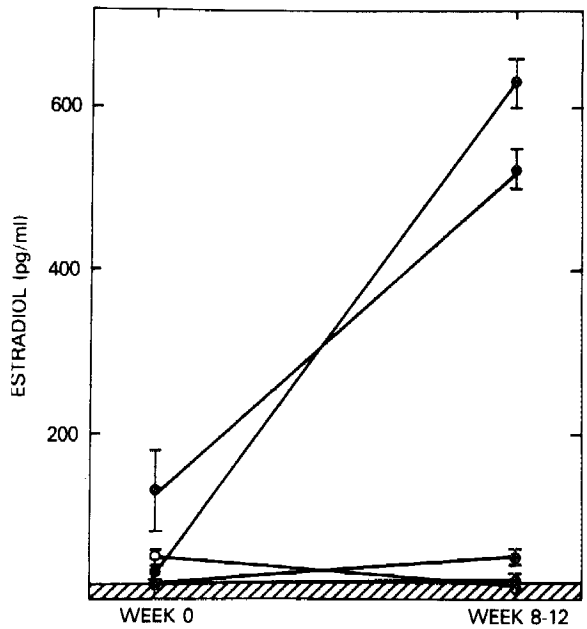


FIG. 3. Plasma estradiol concentrations before therapy and 8–12 weeks after initiation of $LHRH_a$ therapy. ●– –●, Patients 1–5; ○– –○, patient 6. The *hatched area* represents the detection limit of the assay.

TABLE 2. Plasma estradiol and serum gonadotropin concentrations during $LHRH_a$ treatment

| Patient no. | Week | Treatment[a] | Estradiol (pg/ml) | LH (mIU/ml) | FSH (mIU/ml) |
|---|---|---|---|---|---|
| 2[b] | 0 | None | <20 | 1.4 ± 0.1[c] | 3.0 ± 0.4[c] |
| | 8 | $LHRH_a$ | 633 ± 24[c] | 1.6 ± 0.1 | 0.4 ± 0.1 |
| | 16 | None | 64 ± 4 | 1.4 ± 0.1 | 0.2 ± 0.4 |
| | 28 | $LHRH_a$ | 31 ± 3 | 1.6 ± 0.3 | 0.2 ± 0.1 |
| | 40 | $LHRH_a$ | <20 | 2.7 ± 0.1 | 1.1 ± 0.4 |
| | 52 | $LHRH_a$ | 279 ± 12 | 2.7 ± 0.1 | 1.1 ± 0.1 |
| | 62 | $LHRH_a$ | 55 ± 8 | 3.1 ± 0.1 | 1.4 ± 0.02 |
| 4 | 0 | None | 133 ± 22 | 1.0 ± 0.3 | 0.2 ± 0.1 |
| | 8 | $LHRH_a$ | 525 ± 54 | 4.7 ± 0.4 | 0.7 ± 0.2 |
| | 26 | $LHRH_a$ | 135 ± 9 | 4.7 ± 0.2 | 0.8 ± 0.1 |

[a] Indicates the therapy administered from the time of the preceding evaluation until after the completion of sampling.
[b] Data from this patient has been described previously (20).
[c] Mean ± SEM.

TABLE 3. Secondary sexual characteristics after 1 yr of $LHRH_a$ therapy

| Patient no. | Stage of puberty[a] | | | | Menses at 1 yr[b] |
|---|---|---|---|---|---|
| | Breast | | Pubic hair | | |
| | Initial | 1 yr | Initial | 1 yr | |
| 2 | III | III | III | III | + |
| 3 | II | II | II | III | + |
| 4 | II | III | I | I | + |
| 6 | IV | III | III | III | — |

[a] Stage of puberty according to Tanner (24).
[b] +, Present; —, absent.

menses occurred intermittently in patients 2, 3, and 4 (Table 3). Patient 6, however, had regression of secondary sexual characteristics and cessation of menses.

## Discussion

$LHRH_a$ has been used successfully to lower gonadotropin and sex steroid levels and reverse secondary sexual changes, rapid growth, and accelerated bone age advancement in girls with idiopathic true precocious puberty (13–15). Long-acting agonists of LHRH act at the level of the pituitary in humans and decrease secretion of LH and FSH (13–15, 20, 21). These long-acting analogs also inhibit gonadal steroidogenesis in rat systems *in vitro* (22, 23). $LHRH_a$ does not, however, suppress adrenal or gonadal steroidogenesis in humans (20, 21).

The effect of $LHRH_a$ in patients with McCune-Albright syndrome depended on the pretreatment gonadotropin levels. The five patients who had basal and LHRH-stimulated gonadotropin levels within or below the normal prepubertal range had no hormonal or clinical improvement during $LHRH_a$ therapy. The sixth patient, who had pubertal nocturnal gonadotropin levels and a pubertal gonadotropin response to LHRH, had a favorable hormonal and clinical response to $LHRH_a$ similar to that in girls with idiopathic precocious puberty (13–15).

Two girls (patients 2 and 4) had cyclical increases in estradiol while receiving $LHRH_a$. This indicates that although $LHRH_a$ may inhibit ovarian estrogen secretion in rats, the inhibition is not sufficient to suppress ovarian estrogen secretion in these girls with McCune-Albright syndrome.

The underlying mechanism of puberty in patients with McCune-Albright syndrome is unclear. The majority of girls with McCune-Albright syndrome have precocious pseudopuberty independent of pubertal activation of the hypothalamic pituitary-ovarian axis (2–8, 12, 20). Five of the six patients with McCune-Albright syndrome reported in this study had nocturnal levels of serum gonadotropins that were below the levels in prepubertal controls. $LHRH_a$ treatment caused no further suppression of these low gonadotropin levels. Patients 2, 3, and 4 were treated with $LHRH_a$ for 1 yr because of the possibility that ovarian function might be responding to intermittent gonadotropin stimulation that was not evident at the initial evaluation. Despite therapy, these patients had elevations of plasma estradiol levels in the absence of detectable changes in serum gonadotropins. The failure of these girls with McCune-Albright syndrome to respond to $LHRH_a$ therapy provides further evidence that the mechanism of the precocious puberty in most patients with the McCune-Albright syndrome differs from that in patients with true precocious puberty.

The one girl with McCune-Albright syndrome (patient 6) who had evidence of true puberty, with pulsatile nocturnal gonadotropin secretion and a LH-predominant response to LHRH, had an excellent clinical response to $LHRH_a$. Thus, a trial of $LHRH_a$ therapy in such patients appears warranted. If girls with McCune-Albright syndrome have prepubertal or suppressed gonadotropin concentrations and a FSH-predominant response to stimulation with LHRH, treatment with $LHRH_a$ is unlikely to be of benefit.

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